

12/10/2001 14:18

8004215585

REEDFAX

PAGE 05/05

PATENT SPECIFICATION

NO DRAWINGS

1,182,320

Inventors: ROLF WILHELM PFIRRMANN and EMIL HOFSTETTER

Date of filing Complete Specification: 23 Dec. 1968.

Application Date: 21 Dec. 1967.

No. 58,140/67.

Complete Specification Published: 25 Feb. 1970.

Index at acceptance:—C2 C(20Y, 22Y, 220, 227, 29Y, 29X, 30Y, 32Y, 321, 323, 34Y, 342, 36Y, 360, 361, 366, 368, 437, 591, 62X, 620, 623, 628, 630, 65X, 650, 660, 668, 732, 79Y, 790, KJ, LD, LQ); A5 B(20Y, 20X, 27Y, 273, 28Y, 280, 36Y, 360, 361, 362, 363, 364, 38Y, 382, 393, 40Y, 401, 402, 403, 41Y, 411, 50Y, 501, 503, 54Y, 542, 56Y, 566)

Int. Cl.:—C 07 d 51/30

COMPLETE SPECIFICATION

Dihydroorotic and Salts

We, ED. GEISTLICH SÖHNE A.G., a Swiss Body Corporate, of Wolhusen, Lucerne, Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel chemical compounds of use in geriatrics.

Orotic acid, uracil-4-carboxylic acid, was isolated from milk for the first time in 1904 and has been found to be of importance in purine metabolism. In fact in both the young and the aging organism orotic acid plays a central role in protein and purine metabolism and is thus employed in geriatrics both as the free acid and also as salts such as magnesium orotate.

It exerts a liver-protecting activity by formation of nucleic acids in the liver cells which may be detected by normal protein synthesis. Orotic acid also possesses a useful cholesterol-lowering activity, reducing the deposition of lipoids in the coronary artery, the aorta and other blood vessels. It has also been found that dihydroorotic acid possesses similar properties.

We have now found that aliphatic amines carrying a hydrophilic group such as a hydroxyl or amide group form salts with dihydroorotic acid which possess several advantages over the free acid or its metal salts.

These salts are surprisingly stable and without difficulty form 10-20% aqueous solutions whereas free dihydroorotic acid is substantially insoluble in cold water and the metal salts only sparingly soluble. Aqueous solution of the salts of the present invention of up to 50% have, in fact, been prepared.

Further, the new salts show very low toxicity and a good physiological compatibility, particularly compatibility in the stomach. In our investigations, they have

shown a relatively constant blood-level and an improved diffusion ratio and improved the capillary blood flow and generally promoted an easier flow of blood through the vascular system. The new salts have also been found to produce improvements in depth of sleep, in the level of depression and exhaustion and general condition and alertness.

According to the present invention therefore we provided salts of dihydroorotic acid with primary, secondary or tertiary aliphatic amines, said amines having in the molecule at least one other hydrophilic group as defined hereinafter.

The term 'aliphatic amine' as used herein refers to amines in which an aliphatic group is directly bonded to a substituted or unsubstituted amino group: the aliphatic grouping may carry, besides the specified hydrophilic groups, other groups such as aryl groups.

Suitable hydrophilic groups according to the present invention comprise hydroxy; esterified hydroxy e.g. p-amino-benzoxoy; carboxy; amino and carbamoyl groups. Where two or more hydrophilic groups are present in the molecule they may be the same or different.

Preferred amines for salt-formation according to the present invention are aminoethanol and mono- and dialkylaminoethanols, particularly methylaminoethanol, ethylaminoethanol, dimethylaminoethanol, diethylaminoethanol and methyl-ethylaminoethanol.

Other useful amines include β -diethylaminobutyranilide and procaine.

Particularly preferred salts according to the present invention are the aminoethanol salts of dihydroorotic acid, especially dimethylaminoethanol dihydroorotate. These in particular show very low toxicity, the LD₅₀

[Price 5s.]

12/10/2001 14:16 9004215585

REEDFAX

PAGE 02/05

2

1,182,320

2

of diethylaminoethanol dihydroorotate in rats and mice being over 5000 mg/kg.

According to a further feature of the present invention we provide a process for the preparation of the new salts according to the invention comprising reacting dihydroorotic acid or a salt thereof with a primary, secondary or tertiary aliphatic amine carrying at least one further hydrophilic group as defined above or a salt thereof whereby the amine dihydroorotate is formed.

Preferably the acid and amine are heated together with or without an added solvent. The molar ratio may conveniently be 1:1 or an excess of the amine may be used. The added solvent may, for example, be water or an organic solvent such as an alkanol e.g. methanol, ethanol or isopropanol; an ester e.g. ethyl acetate or amyl acetate; a cyclic ether e.g. dioxan or tetrahydrofuran, or a substituted amide e.g. dimethylformamide or dimethylacetamide. The crystalline salt may then be isolated, for example, by concentration of the reaction mixture, e.g. under vacuum.

According to a further feature of the present invention, we provide pharmaceutical compositions comprising, as active ingredient, at least one of the compounds according to the invention in association with a pharmaceutical carrier or excipient. The compositions may be presented in a form suitable for oral, rectal, topical or parental administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of granules, tablets, coated tablets, effervescent tablets, capsules, syrups, emulsions, suspensions or drops, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art. Thus, for example, suitable tableting excipients include lactose, potato and soluble starches and magnesium stearate.

For parenteral administration, the carrier may be a sterile, parenterally acceptable liquid such as sterile water, or a parenterally acceptable oil, e.g. arachis oil, contained in ampoules. Compositions for rectal administration may take the form of suppositories, the carrier comprising a suppository base.

Compositions for topical application may, for example, take the form of creams, ointments or lotions.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, effervescent tablets, capsules, suppositories and

ampoules are examples of suitable dosage unit forms. Each dosage unit preferably contains 10.0 to 200.0 mg, and advantageously 20.0 to 50.0 mg of active ingredient especially 25 mg.

The compositions according to the present invention may further contain other useful physiologically active ingredients for example, vitamins, minerals, amino acids or enzymes.

Vitamins can be added readily to creams, especially creams consisting of water-oil emulsions. Vitamins A, D, E, and K, are soluble in the oil phase while vitamins B₁, B₂, B₆, B₁₂ and C are soluble in the aqueous phase. The dialkylaminoethanol dihydroorotates can well be added to the cream in the aqueous phase.

The dihydroorotate salts are absorbed from the skin and cause increased circulation of the blood. This effect is increased by addition of vitamins and enzymes or enzyme systems such as phosphatases, which influence the cell respiration favourably. Particularly useful materials containing enzymes are placenta-extracts from cows, sheep and pigs and also human placenta extracts. These should be extracted at the lowest temperature possible (not about 40°C). At this temperature, the natural enzyme system will not be destroyed.

Such creams successfully influence symptoms of age appearing on the surface area of the body. The skin becomes smoother, shrinking of the skin due to water losses is checked and the metabolic products in the form of pigments on the skin are at least partly eliminated. Also, deep-seated spasms and muscle pains of the rheumatic type are favourably influenced by creams of this type.

The preferred concentration of the active dihydroorotate in such topical formulations is 0.01 to 1% by weight preferably about 0.1%.

The following examples illustrate the preparation of compounds according to the invention, and also pharmaceutical compositions containing such compounds as active ingredients:—

Example 1

2-Diethylaminoethanol-dihydroorotate

0.79 g of dihydroorotic acid were suspended in 30 ml. of ethanol and 0.67 ml. of diethylaminoethanol were added. The mixture was heated at 70°C until the dihydroorotic acid formed a clear solution. The reaction mixture was filtered hot and evaporated to dryness *in vacuo* at 50-40°C.

Yield: 1.4 g of dihydroorotate; readily soluble in water.

Found:

C, 48.01 H, 8.00 N, 15.52%
C₁₁H₂₁N₃O₃ (275.30) requires: C, 47.99 H, 7.69 N, 15.27%

10/10/2001 14:10 0004215565

REEDFAX

PAGE 03/05

3

1,182,320

3

Example 2***β-Diethylaminobutyranilide dihydroorotate***

0.79 g. of dihydroorotic acid was suspended in 30 ml of ethanol and 1.17 g.

of β-diethylaminobutyranilide. The reaction mixture was then heated to 70°C until a clear solution was formed. This warm solution was filtered and concentrated to dryness *in vacuo* at 40°C.

10

Yield: 1.9 g of dihydroorotate; readily soluble in water.

Found: C, 58.90 H, 7.58 N, 13.82%
C₁₉H₂₃N₃O₅ (392.45) requires: C, 58.14 H, 7.19 N, 14.28%

Example 3***Procaine dihydroorotate***

0.79 g. of dihydroorotic acid were suspended in 30 ml of ethanol and 1.18 g. of

procaine base added. The whole was refluxed for 20 minutes until a clear solution was formed. This hot solution was filtered and evaporated to dryness *in vacuo*.

15

Yield: 1.8 g. of dihydroorotate; readily soluble in water.

Found: C, 54.84 H, 6.68 N, 14.36%
C₁₈H₂₀N₄O₅ (394.42) requires: C, 54.81 H, 6.64 N, 14.21%

20

Example 4***Dimethylaminoethanol dihydroorotate***

1.58 g. dihydroorotic acid were suspended in 50 ml ethanol and 1 ml dimethylaminoethanol was added. The reaction mixture was then heated at 70°C for 5-10 minutes to yield a clear solution. After

filtration the alcoholic solution was evaporated to dryness under reduced pressure at not more than 40°C to yield the desired dihydroorotate (Yield: 2.3 g.). The product is readily soluble in water, and is hygroscopic; taking up one molecule of water of crystallisation.

30

Melting point (120°C) 150-160°C (decomposition)

Found: C, 43.70 H, 6.96 N, 17.06%
C₉H₁₁N₃O₅ (247.23) requires: C, 43.72 H, 6.93 N, 17.00%
Found: C, 41.13 H, 6.88 N, 15.84%
C₉H₁₁N₃O₅ · H₂O requires: C, 40.89 H, 7.18 N, 15.82%

35

Example 5 Capsules

Each capsule contains:
dimethylamino-ethanol
dihydroorotate

vitamin A	25 mg
vitamin B ₁	10,000 i.u.
vitamin B ₂	10 mg
vitamin B ₆	3 mg
vitamin B ₁₂	5 mg
nicotinamide	5 mcg
Panthenol	10 mg
vitamin C	10 mg
vitamin D ₃	70 mg
vitamin E	400 i.u.
calcium (as monohydrogen phosphate)	15 mg
magnesium (as orotate)	25 mg
iron (as fumarate)	7 mg
manganese (as sulphate)	6.5 mg
phosphorus (as calcium monohydrogen phosphate)	0.5 mg
copper (as sulphate)	19 mg
zinc (as sulphate)	1 mg
calcium magnesium inositol hexaphosphate	1 mg
rutine	50 mg
adenosine	10 mg
choline bitartrate	1 mg
	50 mg

The ingredients are mixed together and filled into capsule shells.

Example 6 Effervescent tablets.

Each tablet contains:

dimethylaminoethanol dihydroorotate	25 mg
vitamin A	10,000 i.u.
vitamin B ₁	10 mg
vitamin B ₂	3 mg
vitamin B ₆	5 mg
vitamin B ₁₂	5 mcg
nicotinamide	10 mg
calcium pantothenate	10 mg
vitamin C	70 mg
vitamin D ₃	400 i.u.
vitamin E	15 mg
calcium (as glycerophosphate)	19 mg
magnesium (as orotate)	7 mg
iron (as carbonate saccharate)	2 mg
manganese (as sulphate)	0.5 mg
phosphorus (as calcium glycerophosphate)	15 mg
copper (as sulphate)	1 mg
zinc (as sulphate)	1 mg
calcium magnesium inositol hexaphosphate	50 mg
rutine	10 mg
adenosine	50 mg
choline bitartrate	50 mg

The ingredients are mixed with an effervescent tablet base and pressed into tablets.

10/12/2001 14:10 5304215585

REEDFAX

PAGE 04/05

4

1,182,320

4

Example 7 Cream containing 0.1% di-methylaminoethanol dihydroorotate.

Component A) 100.0 g Hide fat
120.0 g Gezetan E*
40.0 g Lanolin B.P.
1.5 g Propyl p-Hydroxybenzoate B.P.

Component B) 489.0 g Water
50.0 g Glycerine
2.0 g Sorbic acid
1.0 g Dimethylaminoethanol dihydroorotate

Component C) 200.0 g Oil-soluble placenta extract

Component A is heated to melting on the water bath, cooled to 40°C and warmed with stirring still at 40°C with Component B. The temperature should not be allowed to exceed 40°C. Component C is then added, stirred until cool and finally triturated 3 times in a roll mill.

* Non-ionic wax-like oil-in-water type emulsifying agent with added saturated fatty alcohol.

WHAT WE CLAIM IS:—

1. Salts of dihydroorotic acid with primary, secondary or tertiary aliphatic amines, said amines having at least one other hydrophilic group in the molecule, said hydrophilic groups comprising hydroxy, esterified hydroxy, carboxy, amino or carbamoyl groups.

2. Compounds as claimed in claim 1 in which the amines are amino-ethanol and mono- and dialkylaminoethanols.

3. Compounds as claimed in claim 2 in which the amines are methylaminoethanol, ethylaminoethanol, dimethylaminoethanol, diethylaminoethanol and methylethylaminoethanol.

4. Dimethylaminoethanol dihydroorotate.

5. Diethylaminoethanol dihydroorotate.

6. Salts of dihydroorotic acid specifically as herein described, other than dimethylaminoethanol dihydroorotate and diethylaminoethanol dihydroorotate.

7. A process for the preparation of compounds as claimed in claim 1, comprising reacting dihydroorotic acid, or a salt thereof, with a primary, secondary or tertiary aliphatic amine carrying at least one further hydrophilic group as defined in claim 1, or a salt thereof whereby the amine dihydroorotate is formed.

8. A process as claimed in claim 7 in which

the acid and amine are heated together.

9. A process as claimed in claim 8 in which the reaction is effected in an added solvent.

10. A process as claimed in claim 9 in which the solvent is water or an alkanol, an ester, a cyclic ether or a substituted amide.

11. A process as claimed in claim 10 in which the solvent is methanol, ethanol, isopropanol, ethyl acetate, amyl acetate, dioxan, tetrahydrofuran, dimethylformamide or dimethylacetamide.

12. A process as claimed in any of claims 7 to 11 in which the molar ratio of amine to acid is 1 : 1, or an excess of the amine is used.

13. A process as claimed in claim 7 substantially as herein described.

14. A process as claimed in claim 7 substantially as herein described in any of Examples 1 to 15.

15. Pharmaceutical compositions comprising at least one compound as claimed in claim 1 in association with a pharmaceutical carrier or excipient.

16. Compositions as claimed in claim 15 in a form suitable for oral, rectal, topical or paracutaneous administration.

17. Compositions as claimed in claim 16 in the form of granules, tablets, coated tablets, effervescent tablets, capsules, syrups, emulsions, suspensions, drops, ampoules, creams, lotions, ointments or suppositories.

18. Compositions as claimed in claim 15 in the form of dosage units.

19. Compositions as claimed in claim 18 containing 10 to 200 mg of active ingredient per dosage unit.

20. Compositions as claimed in claim 18 containing 20 to 50 mg of active ingredient per dosage unit.

21. Compositions as claimed in any of claims 15 to 20 further containing other useful physiologically active ingredients.

22. Compositions as claimed in claim 21 in which the further ingredients are vitamins, minerals, amino acids or enzymes.

23. Compositions as claimed in claim 15 substantially as herein described.

24. Compositions as claimed in claim 15 substantially as herein described in Example 16 or Example 17.

For the Applicants:
FRANK B. DEHN & Co.,
Chartered Patent Agents,
Imperial House, 15-19 Kingsway,
London, W.C.2.

(7152)

Printed by Her Majesty's Stationery Office Press, Edinburgh, 1970.
Published by The Patent Office, 25 Southampton Buildings, London, W.C.2,
from which copies may be obtained.

T7716

ALLEN TRANSLATION SERVICE
Translated from German

1

- (19) European Patent Office
- (11) Publication number: 0 396 857
A1
- (12) EUROPEAN PATENT APPLICATION
- (21) Application number: 90102853.0
- (22) Application date: 02.14.90
- (51) Int. Cl.⁵: A61K 7/48, A61K 7/06
- (30) Priority: 04.15.89 GERMANY 3912477
- (43) Date of publication of the application:
11.14.90; Patent Bulletin 90/46
- (84) Designated treaty nations:

AUSTRIA, BELGIUM, SWITZERLAND, GERMANY, SPAIN, FRANCE, GREAT BRITAIN,
GREECE, ITALY, LIECHTENSTEIN, LUXEMBOURG, THE NETHERLANDS, SWEDEN
- (71) Applicant: AZUCHEMIE, DR. MED. R. MÜLLER GMBH
Dieselstrasse 5
D-7016 Gerlingen (GERMANY)
- (72) Inventor: Dr. Robert Müller
Herdweg 101
D-7000 Stuttgart (GERMANY)
- (74) Agents: Heinz Nöth, Dipl.-Phys., et al.
Pfenning, Meinig & Partners, patent attorneys
Mozartstrasse 17
D-8000 Munich 2 (GERMANY)
- (54) Externally applicable preparation and its use
- (57) An externally applicable preparation with a quantity therein of deanol or its conventional salts and esters as well as conventional formulation excipients for use, in particular, as skin care agents for improving the structure of the skin and the elasticity of the skin, and to combat premature aging and premature wrinkling of the skin, and also as an oil for use in sporting activities, as a massage oil and as a skin functioning oil as well as hair growth agents and agents to combat hair loss.

EP 0 396 857 A1

2

Externally applicable preparation and its use

The invention pertains to a cosmetic preparation which is applicable to the skin and which is characterized in accordance with the invention by a quantity therein of 2-dimethylaminoethanol (deanol), especially its salts or esters.

In this connection, the deanol can preferably be used in the form of its citrate, hydrogencarbonate, orotate, (RR)-hydrogentartrate, L-hydrogenglutamate, aceglutamate, 4-acetamidobenzoate, hydrogensuccinate, etc.

The internal application of deanol as a psycho-pharmacological preparation or psycho-energetic preparation and as a geriatric preparation has been known medicinally for decades, and is conventional. The alcoholic form is preferred for injection solutions; for capsules, tablets or sugar-coated tablets, use is preferably made of deanol in the form of its salt or ester of organic acids. The situation is different in the case of combination preparations in which deanol is present in e.g. the form of deanol hydrogentartrate, deanol orotate, deanol citrate, deanol aceglutamate and other ester-like and salt-like compounds in combination with mineral substances, various vitamins or even organic acids, such as e.g. orotic acid, which is contained in milk, and other substances such as adenosine, rutin and other materials. In geriatric practice, internal application takes place for the treatment and prevention of age-induced degeneration phenomena.

Usage takes place predominantly on the basis of empirical experience since the actual biochemical mechanism for its action is not known and a certain cholinergic action is assumed to some extent together with a stimulating action, to some extent, on the central nervous system.

Since deanol or its compounds, such as its salts and esters, are used exclusively internally in the geriatric sector in the form of geriatric preparations or in the form of psycho-pharmaceutical preparations, it was completely surprising and unexpected to find an impressive and favorable effect on the consistency of the skin in the case of cosmetic application thereto, including the tissue regions that form part of it.

Cosmetic cremes, ointments, gels, lotions or liquids, oils for sporting use, massaging oils and skin functioning oils which contain deanol or the compounds that have been described can be used as the externally applicable preparation.

In this regard, a favorable effect on the consistency of the skin arises from its application. The elasticity of the skin and the structure of the skin are improved, and premature aging and wrinkling are prevented so that the skin, in total, appears fresher and more youthful. In the case of local application of liquid forms of preparation e.g. in the form of a hair tonic or hair tincture, one finds a reduction in hair loss that is caused androgenetically. The preparations are applied and massaged in conventionally.

A partial explanation of the favorable effect on the various regions of the skin has been found in the meantime via studies according to which, for example, protein synthesis is increased in cell cultures in vitro via the addition of deanol. It has been possible to show in this connection that prolongation of the life span of mitotic and post-mitotic human skin fibroblasts is induced by deanol orotate. The presence and cellular effects of deanol or deanol orotate are a decisive factor in this regard.

EP 0 396 857 A1

3

In the following sections, examples of embodiments are indicated for the various preparations.

1. 100 g of lotion contain:		
Polyoxyethylene stearyl alcohol		2.200 g
Polyoxyethylene fatty acid ester		3.80 g
Deanol orotate		0.65 g
Medium chain length triglycerides		4.00 g
Liquid paraffin	Propylene	6.00 g
glycol		4.00 g
Preservatives		as required
Perfumes		as required
Purified water		up to 100.00 g

2. 100 g of oil for sporting and massage applications contain:		
Neutral oil		60.00 g
Isopropyl myristate		20.00 g
Perfumes		as required
Oxidation inhibitor		as required
Deanol orotate		0.600 g
Paraffin oil		up to 100.00 g

3. 100 g of hair tonic contain:		
[Ethyl] alcohol		40.00 g
Perfumes		as required
Deanol orotate		1.0 g
Purified water		up to 100.00 g

4. 100 g of ointment contain:		
Emulsifying cetyl stearyl alcohol		15.00 g
Oleyl olcate		7.00 g
Medium chain length triglycerides		5.0 g
Propylene glycol		4.00 g
Deanol orotate		1.00 g
Preservatives		as required
Perfumes		as required
Purified water		up to 100.00 g

EP 0 396 857 A1

4

5. 100 g of creme contain:	
Polyoxyethylene fatty acid ester	5.00 g
Liquid paraffin	9.00 g
Medium chain length triglycerides	5.00 g
Stearic acid	4.00 g
Cetyl alcohol	2.00 g
Propylene glycol	4.00 g
Deanol orotate	0.50 g
Preservatives	as required
Perfumes	as required
Purified water	up to 100.00 g

The salts and esters of deanol, which are indicated above as examples, can also be used instead of the orotate. The Na salts, Ca salts or K salts are preferably used as the salts.

Claims

1. Externally applicable preparation, characterized by a quantity therein of 2-dimethylaminoethanol as well as conventional formulation excipients.
2. Preparation in accordance with Claim 1, characterized by the feature that the 2-dimethylaminoethanol is used in the form of a salt or ester.
3. Preparation in accordance with Claim 1 or 2, characterized by the feature that the 2-dimethylaminoethanol is used in the form of its hydrogencarbonate, citrate, orotate, hydrogentartrate, aceglutamate, acetamidobenzoate, or hydrogensuccinate.
4. Preparation in accordance with one of the Claims 1 through 3, characterized by the feature that it is present in the form of ointments, cremes, gels, lotions, oils or other liquids as well as hair tonics and hair tinctures.
5. Use of a preparation in accordance with one of the Claims 1 through 3 as a cosmetic care agent.
6. Use of a preparation in accordance with Claim 5 for improving the consistency of the skin, the structure of the skin and the elasticity of the skin, and to combat premature aging and premature wrinkling of the skin.
7. Use of a preparation in accordance with one of the Claims 1 through 3 in liquid form to combat hair loss and for promoting deficient hair growth.
8. Use of a preparation in accordance with one of the Claims 1 through 6 as an oil for sporting applications, as a massage oil and as a hair functioning oil.

EP 0 396 857 A1

5

European Patent
OfficeApplication number
EP 90 10 2853

EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED PERTINENT		Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication, where appropriate, of relevant passages		
X	GB-A-1 182 320 (R.W. PFIRRMANN) * Patent claims 1, 2, 3, 15, 16, 17; page 2, column 2, lines 93-99 *	1, 2, 3, 1, 4.6	A 61 K 7/48 A 61 K 7/06
A	DE-A-2 131 946 (MARTIN STORTO) * Patent claim 4 *	1	
A	"Martindale - The extra Pharmacopoeia", Edition 28, 1982, page 1700, Compound 12.624-S, The Pharmaceutical Press, London, GB * The entire document *	1,2,3	
			<hr/> TECHNICAL AREAS SEARCHED (Int Cl 5) <hr/> A 61 K
The present search report has been drawn up for all claims.			
Place of search THE HAGUE		Date of completion of search 08-21-1990	Examiner SIERRA GONZALEZ M.T.
CATEGORY OF DOCUMENTS CITED			
X:	Particularly pertinent on its own terms	T:	Theory or principle underlying the invention
Y:	Particularly pertinent in combination with another document belonging to the same category	E:	Patent document with a date prior to the filing date, which had not only been published on the filing date or on a subsequent date.
A:	Pertinent in consideration of at least one claim or the general technological background	D:	Cited in application
O:	Non-written disclosure	L:	Cited for other reasons
P:	Inserted document.	&:	Member of the same family, related document.

OCT 08 '01 13:58 FR J&J-PATENT LAW

732 524 5889 TO 919732923954

P.02/06

T 1716



⑪ Veröffentlichungsnummer: **0 396 857 A1**

⑫ **EUROPÄISCHE PATENTANMELDUNG**

⑬ Anmeldenummer: 90102853.0

⑭ Int. Cl.⁸: **A61K 7/48, A61K 7/06**

⑮ Anmeldetag: 14.02.90

⑯ Priorität: 15.04.89 DE 3912477

⑰ Veröffentlichungstag der Anmeldung:
14.11.90 Patentblatt 90/46

⑱ Benannte Vertragsstaaten:
AT BE CH DE ES FR GB GR IT LI LU NL SE

⑲ Anmelder: **AZUCHEMIE, DR. MED. R. MÜLLER GMBH**
Dieselstrasse 6
D-7016 Gerlingen(DE)

⑳ Erfinder: **Müller, Robert, Dr.**
Herdweg 101
D-7000 Stuttgart(DE)

㉑ Vertreter: **Nöth, Heinz, Dipl.-Phys. et al**
Patentanwälte Pfenning, Meinig & Partner
Mozartstrasse 17
D-8000 München 2(DE)

㉒ **Äusserlich anzuwendendes Präparat und seine Verwendung.**

㉓ Ein äusserlich anzuwendendes Präparat mit einem Gehalt an Deanol bzw. dessen gebräuchlichen Salzen oder Estern sowie üblichen Formulierungshilfsstoffen, insbesondere für die Verwendung als Hauptpflegemittel zur Verbesserung der Hautstruktur und Hautelastizität, gegen vorzeitiges Altern und vorzeitige Faltenbildung der Haut, ferner als Sport-, Massage- und Hautfunktionsöl sowie Haarwuchsmittel und Mittel gegen Haarausfall.

EP 0 396 857 A1

EP 0 396 857 A1

Äußerlich anzuwendendes Präparat und seine Verwendung

Die Erfindung betrifft ein auf der Haut anzuwendendes kosmetisches Präparat, das erfindungsgemäß gekennzeichnet ist durch einen Gehalt an 2-Dimethyl-aminoethanol (Deanol), insbesondere seiner Salze oder Ester.

Das Deanol kann dabei bevorzugt als Citrat, Hydrogencarbonat, Orotat, (RR)-hydrogentartrat, L-hydroxyglutamat, Aceglutamat, 4-acetamidobenzoat, Hydrogensuccinat usw. verwendet werden.

Die innerliche Anwendung von Deanol als Psychopharmakon bzw. Psychoenergetikum und als Geriatrikum ist seit Jahrzehnten medizinisch bekannt und üblich. Für Injektionslösungen wird bevorzugt die alkoholische Form, für Kapseln, Tabletten oder Dragees die Form von Deanol als Salz bzw. Ester organischer Säuren eingesetzt. Verschiedentlich handelt es sich auch um Kombinationspräparate, bei denen Deanol z. B. als Deanol-hydrogentartrat, Deanol-orotat, Deanol-citrat, Deanol-aceglutamat und anderen ester- oder salzartigen Verbindungen in Kombination mit Mineralstoffen, verschiedenen Vitaminen oder auch organischen Säuren, wie z. B. der in der Milch enthaltenen Orotsäure, und anderen Stoffen, wie Adenosin, Rutin und anderen, vorliegt. In der Geriatrie erfolgt die innerliche Anwendung zur Behandlung und Vorbeugung von altersbedingten Abnutzungserscheinungen.

Die Anwendung erfolgt vorwiegend aufgrund empirischer Erfahrungen, da der eigentliche biochemische Wirkungsmechanismus nicht bekannt ist und teils eine gewisse cholinergische, teils eine stimulierende Wirkung auf das zentrale Nervensystem angenommen wird.

Nachdem Deanol bzw. seine Verbindungen, wie Salze oder Ester, ausschließlich innerlich im Bereich der Geriatrie als Geriatrika oder als Psychopharmaka zur Anwendung kommen, hat sich nunmehr in völlig überraschender und unerwarteter Weise gezeigt, daß bei externer kosmetischer Anwendung auf der Haut ein eindrucksvoller günstiger Effekt auf deren Beschaffenheit, einschließlich dazugehöriger Gewebsbezirke, resultiert.

Als äußerlich anzuwendende Zubereitung können kosmetische Cremes, Salben, Gele, Lotionen bzw. Liquida, Sport-, Massage- und Hautfunktionsöle, welche Deanol bzw. die beschriebenen Verbindungen enthalten, verwendet werden.

Hierbei kommt es unter der Anwendung zu einem günstigen Einfluß auf die Hautbeschaffenheit. Die Hautelastizität und die Hautstruktur werden verbessert und vorzeitiger Alterung und Faltenbildung vorgebeugt, so daß die Haut insgesamt frischer und jugendlicher erscheint. Bei lokaler Anwendung flüssiger Zubereitungsformen, z. B. als Haarwasser oder Haartinktur, kommt es zu einer Verminderung von androgenetisch bedingtem Haarausfall. Die Präparate werden üblicherweise aufgetragen und einmassiert.

Eine teilweise Erklärung für den günstigen Effekt auf die Hautbezirke findet sich inzwischen durch Untersuchungen, wonach z. B. in vitro durch Zugabe von Deanol die Proteinsynthese in Zellkulturen erhöht wird. Hierbei konnte gezeigt werden, daß z. B. durch Deanol-orotat eine Verlängerung der Lebensspanne mitotischer und postmitotischer menschlicher Hautfibroblasten induziert wird. Entscheidend kommt es hierbei auf die Anwesenheit und zelluläre Beeinflussung durch Deanol bzw. Deanol-orotat an.

Im folgenden werden Ausführungsbeispiele für verschiedene Zubereitungen angegeben.

1. 100 g Lotion enthalten:	
Polyoxyethylenstearylalkohol	2,200 g
Polyoxyethylenfettsäureester	3,80 g
Deanol-orotat	0,65 g
Mittelkettige Triglyzeride	4,00 g
Paraffinum perliquidum	6,00 g
Propylenglykol	4,00 g
Konservierungsmittel	q.s.
Duftstoffe	q.s.
gereinigtes Wasser	ad 100,00 g

EP 0 398 857 A1

2. 100 g Sport- und Massageöl enthalten:

Neutralöl	60,00 g
Isopropylmyristat	20,00 g
Duftstoffe	q.s.
Oxidationsinhibitor	q.s.
Deanol-rotat	0,600 g
Paraffinöl	ad 100,00 g

3. 100 g Haarwasser enthalten:

Alkohol	40,00 g
Duftstoffe	q.s.
Deanol-rotat	1,0 g
gereinigtes Wasser	ad 100,0 g

4. 100 g Salbe enthalten:

Emulgierender Cetylstearylalkohol	15,00 g
Ölsäureoleylester	7,00 g
Mitteltetige Triglyzeride	5,00 g
Propylenglykol	4,00 g
Deanol-rotat	1,00 g
Konservierungsmittel	q.s.
Duftstoffe	q.s.
gereinigtes Wasser	ad 100,00 g

5. 100 g Creme enthalten:

Polyoxyethylenfettsäureester	5,00 g
Paraffinum perliquidum	9,00 g
Mitteltetige Triglyzeride	5,00 g
Stearinsäure	4,00 g
Cetylalkohol	2,00 g
Propylenglykol	4,00 g
Deanol-rotat	0,50 g
Konservierungsmittel	q.s.
Duftstoffe	q.s.
gereinigtes Wasser	ad 100,00 g

Anstelle des Rotats können auch die oben als Beispiele angegebenen Salze und Ester des Deanols verwendet werden. Als Salze kommen bevorzugt die Na-, Ca- oder K-Salze zum Einsatz.

55 Ansprüche

1. Äußerlich anzuwendendes Präparat, gekennzeichnet durch einen Gehalt an 2-Dimethyl-aminoethanol sowie üblichen Formulierungstoffen.

OCT 08 '01 13:59 FR J&P-PATENT LAW

732 524 5889 TO 919732923954

P.05/06

EP 0 398 857 A1

2. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß das 2-Dimethyl-Aminoethanol als Salz oder Ester eingesetzt ist.

3. Präparat nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das 2-Dimethyl-aminoethanol als Hydrogencarbonat, Citrat, Orotat, Hydrogentartrat, Aceglutamat, Acetamidobenzoat oder Hydrogensuccinat eingesetzt ist.

4. Präparat nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß es in Form von Salben, Cremes, Gelen, Lotionen, Ölen oder anderen Liquida sowie als Haarwässer und Haartinkturen vorliegt.

5. Verwendung eines Präparates nach einem der Ansprüche 1 bis 3 als pflegendes Kosmetikum.

6. Verwendung eines Präparates nach Anspruch 5 zur Verbesserung der Hautbeschaffenheit, der Hautstruktur und Hautelastizität, gegen vorzeitiges Altern und gegen vorzeitige Faltenbildung der Haut.

7. Verwendung eines Präparates nach einem der Ansprüche 1 bis 3 in flüssiger Form gegen Haarausfall und zur Förderung mangelnden Haarwuchses.

8. Verwendung eines Präparates nach einem der Ansprüche 1 bis 6 als Sport-, Massage- und Hautfunktionsöl.



Europäisches
Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 90 10 2853

EINSCHLÄGIGE DOKUMENTE			
Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. CL.5)
X	GB-A-1 182 320 (R.W. PFIRRMANN) * Patentansprüche 1,2,3,15,16,17; Seite 2, Spalte 2, Zeilen 93-99 *	1,2,3,1 4,6	A 61 K 7/48 A 61 K 7/06
A	DE-A-2 131 946 (MARTIN STORTO) * Patentanspruch 4 *	1	
A	"Martindale - The extra Pharmacopoeia", Auflage 28, 1982, Seite 1700, Verbindung 12.624-S, The Pharmaceutical Press, London, GB * Das ganze Dokument *	1,2,3	
			RECHERCHIERTE SACHGEBIETE (Int. CL.5)
			A 61 K
Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt			
Recherchenamt DEN HAAG		Abschlußdatum der Recherche 21-08-1990	Prüfer SIERRA GONZALEZ M.T.
KATEGORIE DER GENANNTEN DOKUMENTE			
X : von besonderer Bedeutung allein betrachtet Y : von besonderer Bedeutung in Verbindung mit einer späteren Veröffentlichung derselben Kategorie A : technologischer Hintergrund O : nichttechnische Offenbarung P : Zwischenliteratur		T : der Erfindung zugrunde liegende Theorien oder Grundsätze E : dieses Patentedokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist D : in der Anmeldung angeführtes Dokument I : aus anderen Gründen angeführtes Dokument d : Mitglied der gleichen Patentfamilie, überwachendes Dokument	

EP 90 10 2853 (P.06)